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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Centers for Disease Control and Prevention

[Docket No. CDC-2017-0117]

**National Health and Nutrition Examination Survey (NHANES)
Stored Biologic Samples; Proposed Cost Schedule and
Guidelines for Proposals to Use Serum, Plasma, and Urine
Samples**

Agency: Centers for Disease Control and Prevention (CDC),
Department of Health and Human Services (HHS).

ACTION: Notice.

SUMMARY: The Centers for Disease Control and Prevention (CDC) in the Department of Health and Human Services (HHS) announces the availability of stored sera, plasma, and urine samples obtained from participants in the National Health and Nutrition Examination Survey (NHANES) for use and the fee schedule for such use. The National Health and Nutrition Examination Survey (NHANES) is one

of a series of health-related surveys conducted by CDC's National Center for Health Statistics (NCHS).

DATES: The stored NHANES biologic samples are available [INSERT DATE OF PUBLICATION IN THE FEDERAL REGISTER].

The fee structure for these samples is effective [INSERT DATE OF PUBLICATION IN THE FEDERAL REGISTER].

FOR FURTHER INFORMATION CONTACT: Dr. Geraldine McQuillan, National Center for Health Statistics, Centers for Disease Control and Prevention, 3311 Toledo Road, Hyattsville, MD 20782. Telephone: 301-458-4371; Fax: 301-458-4029; Email: Serumplasmaurine@cdc.gov

Authority: Sections 301,306 and 308 of the Public Health Service Act (42 U.S.C. 241,242k and 242M).

SUPPLEMENTARY INFORMATION: NHANES is a program of periodic surveys conducted by NCHS. Examination surveys conducted since 1960 by NCHS have provided national estimates of the health and nutritional status of the U.S. civilian non-institutionalized population. The goals of NHANES are: (1) to estimate the number and

percent of persons in the U.S. population and designated subgroups with selected diseases and risk factors; (2) to monitor trends in the prevalence, awareness, treatment and control of selected diseases; (3) to monitor trends in risk behaviors and environmental exposures; (4) to analyze risk factors for selected diseases; (5) to study the relationship between diet, nutrition and health; (6) to explore emerging public health issues and new technologies; and (7) to establish and maintain a national probability sample of baseline information on health and nutrition status.

Samples are available from NHANES III and the continuous NHANES that started in 1999. Approximately 30,000 individuals were examined in NHANES III, which began in the fall of 1988, and ended in the fall of 1994. Researchers can analyze data from this survey in two phases. Phase 1 was conducted from October 1988 to October 1991 and Phase 2 began October 1991 and ended October 1994. Though participants consented to storing samples of their blood and urine for future testing, only research proposals with test results that are judged *not* to have clinical significance for participants will be accepted.

See: <http://www.cdc.gov/nchs/nhanes/nhanes3.htm>, for more information on NHANES III.

Beginning in 1999, NHANES became a continuous, annual survey with examination of approximately 5,000 individuals a year and data release every two years. Samples from a single year of the survey will only be provided in emergency situations (outbreaks). Research projects must use two-year cycles or multiple two year cycles for their research (i.e. 1999-2000, 2001-2002 etc.) In order to assure the representative nature of NHANES at least a 1/3 sample of a two year cycle must be requested for an individual proposal. For details of the sampling design, see the Analytic Guidelines at: <https://wwwn.cdc.gov/nchs/nhanes/analyticguidelines.aspx>.

Starting in 1999, the consent form informed participants that they would not receive results from any future laboratory analysis that may be conducted on their samples. Therefore, only research proposals with laboratory test results that do *not* have clinical significance to the survey participant will be accepted. Clinical significance of a laboratory test will be judged by the technical panel reviewing proposals, and the researcher should address this in the research proposal.

A laboratory analyte is considered clinically significant to the survey participant if the following criteria are met: the findings have significant implications for the participant's health, a course of action is readily available to treat the associated health concern, and laboratory tests are performed by a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory and therefore deemed valid.

Serum, plasma, and urine samples are currently available from NHANES III (conducted from 1988-1994) and from NHANES 1999-2016 (Table A).

Serum, plasma, and urine samples are stored in two biorepositories. Surplus samples that were initially used for laboratory assays included in the surveys, were stored at -70°C and have been through at least two freeze-thaw cycles. They are stored at a commercial biorepository under contract to NCHS. In addition, serum, plasma, and urine samples were also stored immediately after collection at -80°C or below in vapor-phase liquid nitrogen. These samples have not undergone a freeze-thaw cycle and are considered pristine samples.

The CDC and Agency for Toxic Substances and Disease Registry (ATSDR) Sample Packaging and Handling Repository

(CASPIR) is the long-term repository for the pristine NHANES serum, plasma, and urine samples. NCHS is making both of these collections available for research proposals. Proposals that request pristine samples stored at CASPIR should justify the use of the unthawed samples. Please see the NHANES Biospecimen Program series report for details about collection and storage of serum, plasma, and urine samples

http://www.cdc.gov/nchs/data/series/sr_02/sr02_170.pdf.

Table A: Overview of biospecimens by survey year, NHANES III(1988-1994) and NHANES 1999-2014						
NHANES Cycle	Sample Type					
	Pristine ¹			Surplus ²		
	Ser a	Plasma	Urine	Ser a	Plasma	Urine
III (1988-1994)	X			X		
1999-2000	X	X	X	X	X	X
2001-2002	X	X	X	X	X	X
2003-2004	X	X	X	X		
2005-2006	X	X	X	X		
2007-2008	X	X	X	X		
2009-2010	X	X	X	X		
2011-2012	X		X	X		
2013-2014	X		X	X		
2015-2016	X		X	X		

¹BSamples immediately frozen for storage, did not undergo laboratory testing

²Samples were surplus after laboratories had completed testing

Proposal Evaluation

All proposals for use of NHANES samples will be evaluated by a Technical Panel for scientific merit, public health significance, and lack of clinical significance to the participant; by the NCHS Confidentiality Officer for disclosure risk; and by the NCHS Human Subjects Officer and the ERB for any potential human subjects concerns. The NCHS Ethics Review Board (ERB) will review the proposal even if the investigator has received approval by their institutional review panel.

The Technical Panel consists of NHANES staff: two physicians, one statistician and two laboratory experts, other experts from inside or outside the Federal Government are added as needed. The Technical Panel will evaluate the proposal for the scientific, technical and medical significance of the research, the appropriateness and adequacy of the research design, and the methodology proposed to reach the research goals. See 'Criteria for Technical Evaluation of Proposals' below. The proposal should outline how the results from the laboratory analysis will be used. Because NHANES is a complex, multistage probability sample of the U.S. population, the appropriateness of the NHANES sample to address the goals

of the proposal will be an important aspect of scientific merit.

The survey oversamples the two largest race/ethnic minority groups, non-Hispanic blacks and Mexican Americans (and all Hispanics since 2007-08), and, since 2011-2012, Asians. Sampling weights are therefore used to make national estimates of frequencies. The use of weights, sampling frame and methods of assessment of variables included in the data are likely to affect the proposed research. For this reason proposers are required to request at least a 1/3 sample of a NHANES cycle to maintain the representative nature of the survey.

The Technical Panel will also review the data analysis plan and evaluate whether the proposal is an appropriate use of the NHANES samples. The investigators should justify why they need a national probability sample for their research. The Technical Panel will assure that the proposed project does not go beyond either the general purpose for collecting the samples in the survey, or of the specific stated goals of the proposal.

Investigators are encouraged to review the NHANES data, survey documents, manuals and questionnaires at:

http://www.cdc.gov/nchs/nhanes/nhanes_questionnaires.htm

or for NHANES III:

<https://www.cdc.gov/nchs/nhanes/nhanes3/datafiles.aspx>

PROCEDURES FOR PROPOSALS:

All investigators (including CDC investigators) must submit a proposal for use of NHANES serum, plasma, or urine samples. Proposals are limited to a maximum of 10 single-spaced typed pages, excluding figures and tables, using at least a size 10 font 10cpi. The cover of the proposal should include the name, address, and phone number and E-mail address of the principal investigator (PI) and the name of the institution where the laboratory analysis will be done. All proposals should be E-mailed to Serumplasmaurine@cdc.gov. Proposals must include a cover page with the title of the proposal and the name, address, phone number and E-mail address of all investigators. Proposals from CDC investigators must also include investigators scientific ethics verification number.

The following criteria will be used for technical evaluation of proposals:

Proposals should include the following information:

1) Specific Aims: List the broad objectives; describe concisely and realistically what the research is intended to accomplish, and state the specific hypotheses to be tested. NHANES is designed to provide prevalence estimates of diseases or conditions that are expected to affect at least 5-10 percent of the population. Research proposals that expect much lower prevalence estimates need to provide more detail on why samples from NHANES are needed for the project and provide details on how these data will be analyzed.

2) Background and Public Health Significance: Describe the public health significance, scientific merit, and practical utility of the assay. Briefly describe in 1-2 pages the background of the proposal, identifying gaps in knowledge that the project is intended to fill. State concisely the importance of the research in terms of the broad, long-term objectives and public health relevance including a discussion of how the results will affect public health policy or further scientific knowledge. The proposal should justify the need for samples that are representative of the U.S. population. The proposer

should convey how the results will be used and the relationship of the results to the data already collected in NHANES. The analyses should be consistent with the NHANES mission and the health status variables.

3) Research Design and Methods: Describe the research design, analytic plan, and the procedures to be used. A detailed description of laboratory methods including validity and reliability must be included with references. The volume of sample and number of samples requested must be specified. Adequate methods for handling and storage of samples must also be addressed. The laboratory must demonstrate expertise in the proposed laboratory test including the capability for handling the workload requested in the proposal. The proposal should also include a justification for determination of sample size or a power calculation. If the researcher is requesting a sub-sample of samples, a detailed description and justification, must be given. The researcher must describe how this sub-sample will be re-weighted to provide national estimates.

The program will evaluate the Investigator's submitted proposal study design and analysis plan to

determine whether the project is consistent with the design of the NHANES survey. In general, resulting data will be released in the public domain. Released data from sub-samples may be less useful to the research community, so such requests will receive a lower priority for the samples.

4) Clinical Significance of Results: Address the clinical significance to the survey participant of the proposed laboratory test. Since the consent document for sample storage and future studies states that individual results will not be provided to the participant, the investigator must address whether there is definitive evidence that the proposed test results have health implications to the participants and whether knowledge of results would provide grounds for medical intervention (even if many years have passed since the participant was in the survey and the sample collected). Any test with results that are clinically significant, and would require reporting to the participant, is not appropriate for testing on the stored serum, plasma, or urine samples; laboratory testing that is clinically significant should be considered for inclusion in a

concurrent NHANES survey.

5) Qualification: Provide a brief description of the Principal Investigator's expertise in the proposed area, including publications in this area within the last three years. A representative sample of earlier publications may be listed as long as this section does not exceed two pages.

6) Period of Performance: Specify the project time period. Substantial progress must be made in the first year that samples have been obtained, and the project should be completed within a reasonable time period. Please discuss the approximate time the investigator expects this project will take to complete the project.

At the end of the project period, any unused samples must be returned to the NHANES Specimen Repository or discarded. The NCHS Project Officer must be consulted about the disposition of the samples.

7) Funding: The source and status of the funding to perform the requested laboratory analysis should be included. Investigators will be responsible for the cost

of processing and shipping the samples. The cost per sample is \$13.00. The basis for the cost structure is in the last section of this document. Reimbursement for the samples will be collected before the samples are released.

SUBMISSION OF PROPOSALS:

Proposals can be submitted in MS Word format by E-mail to:

Dr. Geraldine McQuillan (see **FOR FURTHER INFORMATION CONTACT**) .

Project Timeframes

- Submitting Proposals: Can be submitted on an ongoing basis
- Scientific Review Date: Within two months of proposal submission
- Institutional Review Date: Within one month of final proposal acceptance
- Anticipated distribution of samples: one month after ERB approval

APPROVED PROPOSALS:

Approved projects will be provided samples after receipt of a signed Materials Transfer Agreement (MTA) and a check (written to The Centers for Disease Control and Prevention) for the cost of the samples or for Federal Government proposals a signed Interagency Agreement (IAA). All laboratory results obtained from the samples must be sent back to NCHS to be linked to the variables requested by the investigator that are needed to perform a quality control review of the data under a signed Data Sharing Agreement or a Designated Agent Agreement. This review must take place within 60 days of the return of the data to NCHS so these data may be released to the public. All files will also undergo disclosure review at NCHS before release.

AGENCY AGREEMENT :

A formal signed agreement in the form of a MTA or an IAA with investigators who have projects approved will be completed before the release of the samples. This agreement will contain the conditions for use of the samples as stated in this document and as agreed upon by the investigators and CDC.

CONTINUATIONS:

A brief progress report will be submitted annually. This will be the basis for the NCHS ERB continuation reports that are required annually. After 5 years of annual continuations, if there is need for continued use of samples to complete the protocol study, a new protocol is required.

DISPOSITION OF RESULTS AND SAMPLES:

No samples provided can be used for any purpose other than those specifically requested in the proposal and approved by the Technical Panel and the NCHS ERB. No samples can be shared with others, including other investigators, unless specified in the proposal and so approved. Any unused samples must be returned to the NHANES Serum, Plasma and Urine Repository or disposed of, after NHANES approval, upon completion of the approved project. These results, once returned to NCHS, will be part of the public domain. The proposer will have 60 days for quality control review of the data before public release.

COST SCHEDULE FOR PROVIDING NHANES SAMPLES:

There is a nominal processing fee of \$13.00 for each sample received from the NHANES Serum, Plasma and Urine Repository. If the investigator requests to use the samples for another project after the completion of the initial project, the cost will be \$5.00 per sample to handle the processing of the data and management of the proposal process. The costs include the collection, storage, and processing of the samples along with the review of proposals and the preparation of the data files. The costs listed are for the recurring laboratory materials to dispense and prepare the samples during collection and for shipping; the computer software needed for the preparation of the data files and for the release of the data along with documentation on the NHANES Web page. See:

https://www.cdc.gov/nchs/nhanes/about_nhanes.htm. Labor costs are based on a proposal administrator and computer programmers at NCHS to prepare the data files. The storage and pulling the samples from the freezer fees include the costs for the NHANES repository.

Fee Schedule for NHANES Biologic Samples

Cost Factors	Cost Per Vial
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Material and Equipment	\$2.85
Processing the samples (Receiving, handling and shipping)	\$2.15
Administrative, management of the proposal process.	\$1.50
Inventory management	\$1.50
Preparation of data files	\$3.50
SUBTOTAL	\$11.50
CDC Support (5%)	\$0.58
SUBTOTAL	\$12.08
NCHS Support (7.50%)	\$0.91
TOTAL	\$13.00*

- Total is rounded up from \$12.99

Date: December 5, 2017

Sandra Cashman,

Executive Secretary,

Centers for Disease Control and Prevention.

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